

Usefulness of the Prostate Health Index in Predicting the Presence and Aggressiveness of Prostate Cancer Among Korean Men

Jae-Yoon Kim

Inje University

Ji-Hyeong Yu

Inje University

Luck-Hee Sung

Inje University

Dae-Yeon Cho

Inje University

Hyun-Jung Kim

Inje University

Soo-Jin Yoo (✉ sjyoo@paik.ac.kr)

Inje University

Research Article

Keywords: prostate health index, prostate specific antigen, prostate cancer, Korean

Posted Date: April 21st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-424241/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

We aimed to evaluate the usefulness of the Beckman Coulter prostate health index (PHI) and compare it with total prostate specific antigen (PSA) and related derivatives in predicting the presence and aggressiveness of prostate cancer (PCa) in the Korean population.

Methods

A total of 140 men who underwent their first prostate biopsy for suspected PCa were included in this prospective observational study. The diagnostic performance of total PSA, free PSA, %free PSA, [-2] proPSA (p2PSA), %p2PSA, and PHI in detecting and predicting the aggressiveness of PCa was estimated using the receiver operating characteristic curve (ROC) and logistic multivariate regression analyses.

Results

Of 140 patients, PCa was detected in 63 (45%), and 48 (76.2%) of them had significant cancer with a Gleason score (GS) ≥ 7 . In the whole group, the area under the curve (AUC) for ROC analysis of tPSA, free PSA, %fPSA, p2PSA, %p2PSA, and PHI were 0.63, 0.57, 0.69, 0.69, 0.71, and 0.75, respectively, and the AUC was significantly greater in the PHI group than in the tPSA group ($p = 0.005$). For PCa with GS ≥ 7 , the AUCs for tPSA, free PSA, %fPSA, p2PSA, %p2PSA, and PHI were 0.62, 0.58, 0.41, 0.79, 0.87, and 0.88, respectively, and the AUC was significantly greater in the PHI group than in the tPSA group ($p < 0.001$). In the subgroup with tPSA 4–10 ng/mL, both %p2PSA and PHI were strong independent predictors for PCa ($p = 0.031$, $p = 0.027$) and significantly improved the predictive accuracy of a base multivariable model including age, tPSA, and %fPSA, using multivariate logistic regression analysis. ($p = 0.015$, $p = 0.010$). Additionally, at a cutoff PHI value >33.4 , unnecessary biopsy could be avoided in 22.9% (32/140) cases, with no aggressive cancer patients missed.

Conclusion

This study shows that %p2PSA and PHI are superior to total PSA and %fPSA in predicting the presence and aggressiveness (GS ≥ 7) of PCa among Korean men. Using PHI, a significant proportion of unnecessary biopsies can be avoided.

Background

Prostate cancer (PCa) is the second most common cancer in the Western population [1].

In Korea, the incidence of PCa has steadily increased and is now the fifth most frequent cause of cancer among men [2]. Several studies have demonstrated that PCa in Korean men shows worse disease characteristics [3]. Kang and colleagues demonstrated that Koreans had higher T stages than their

American counterparts ($p=0.021$) and higher Gleason scores than Americans in all age groups. And Koreans also had higher Gleason scores than Americans for PSA >10 ng/mL ($p<0.05$) in their study.

A large proportion of PCa diagnosed in the Korean population shows poor differentiation compared to its American counterparts [4]. Therefore, the accuracy of diagnosis and risk stratification of PCa using appropriate biomarkers may be more important for suitable treatment in the Korean population.

Total prostate-specific antigen (tPSA) is a widely used tumor marker for the screening, diagnosis, monitoring, and prognosis of prostate cancer worldwide [5]. The introduction of tPSA has resulted in increased early detection of PCa and reduced mortality [6]. In the early diagnosis of PCa using tPSA, the main problem was that the low positive predictive value (PPV) of tPSA resulted in unnecessary biopsies [7]. The positive rate for cancer at biopsy was approximately 25% among the population with PSA levels of 2-10 µg/L.

In addition, PSA cannot accurately identify aggressive PCa, which has clinical significance for treatment. Consequently, the wide application of PSA in detecting PCa has increased concerns about over-diagnosis and over-treatment [8].

Therefore, the development of new biomarkers is needed to improve detection of PCa and to discriminate clinically significant and insignificant PCa.

Several studies have performed PSA isoform assays to overcome the limitations of PSA. Free PSA (fPSA) consists of three different forms: benign PSA, intact inactive PSA, and proPSA. The subfraction of proPSA has several molecular isoforms, [-2], [-4], and [-5, -7] proPSA [9].

Previous studies have demonstrated a significantly increased detection rate for PCa by measuring [-2] proPSA (p2PSA), especially the derivatives %p2PSA (p2PSA/fPSA) and prostate health index (PHI), which is a mathematical combination of tPSA, fPSA, and p2PSA [10, 11]. Additionally, recent studies demonstrated that %p2PSA and PHI showed superior performance to tPSA or %fPSA (fPSA/tPSA) in predicting PCa aggressiveness [12].

The aim of this prospective, observational study was to investigate the usefulness of p2PSA and its derived %p2PSA and PHI in the detection of PCa and to discriminate clinically significant PCa in Korean patients by estimating its ability to avoid unnecessary biopsies.

Methods

The study included consecutive men who underwent their first prostate biopsy between April 2016 and July 2019. The indications for prostate biopsies were any one of the following: serum tPSA > 3.0 ng/mL, presence of palpable nodule on prostate digital rectal examination, and observation of hypoechoic findings on transrectal prostate ultrasonography. Exclusion criteria were medical therapies or procedures that might affect PSA levels, acute prostate inflammation, or urinary tract infection in the 3 months prior

to biopsy. Patients who underwent prostate biopsy or were treated with any 5-alpha-reductase inhibitors were excluded.

Blood samples were collected to measure the pre-biopsy tPSA, fPSA, and p2PSA levels prior to prostate biopsy. The blood was processed to clot for 1 h at room temperature, followed by centrifugation for 15 min. The sera were aliquoted and frozen at -80° C and processed on an Access 2 immunoassay system (Beckman Coulter, Brea, CA, USA) using dedicated Access tPSA, fPSA, and p2PSA reagents. %p2PSA was calculated using the formula $[(\text{p2PSA pg/mL}) / (\text{fPSA ng/mL} \times 1000)] \times 100$, and PHI using the formula $[(\text{p2PSA pg/mL}) / (\text{fPSA ng/mL})] \times \sqrt{\text{tPSA}}$.

The patients then underwent transrectal ultrasound-guided prostate biopsies following a standardized extended scheme with at least 12 biopsy cores obtained from the prostate gland and additional cores taken when other areas were suspected. The specimens were inspected by a genitourinary pathologist who was blinded to the results of the blood test. PCa was confirmed and graded according to the definitions of the International Society of Urological Pathology.

The primary endpoint was comparison of accuracy of the diagnostic performance of %p2PSA and PHI with that of tPSA 0 %fPSA, which are currently widely used biomarkers in detecting PCa at biopsy. The secondary endpoint was the predictive ability of these biomarkers to discriminate aggressive PCa with a Gleason score (GS) ≥ 7 .

Quantitative data are presented as median (interquartile range) and categorical data as numbers (n) and percentages. The normal distribution of variables was assessed using the Kolmogorov-Smirnov test. Student's t-test was used for comparisons of parametric variables, and the Mann-Whitney U-test for non-parametric continuous variables. Bivariate and multivariate logistic regression analyses were used to determine the association between the biomarkers and the presence of PCa in the whole group and subgroup with PSA 4-10 and PCa with GS ≥ 7 at biopsy.

These markers were added to the base multivariate model including age, tPSA, and %fPSA to evaluate the usefulness of %p2PSA and PHI in predicting the presence of PCa. The improvement in predictive accuracy was measured as the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis. The DeLong method was used to compare the statistical differences between the AUCs. Odds ratios (ORs) with 95% confidence intervals were determined.

Statistical analyses were conducted using SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$. AUC comparisons were conducted using MedCalc software 19.4 (MedCalc Software, Mariakerke, Belgium).

The study protocol was approved by the Institutional Review Board (IRB) of the Sanngye Paik Hospital, Inje University. All participants provided written informed consent before participation in the study. All methods were carried out in accordance with relevant guidelines and regulations.

Results

A total of 140 men who underwent their first prostate biopsy with positive or negative prostate biopsy between April 2016 and July 2019 were included in this study. The demographic and clinical characteristics of the study participants are summarized in Table 1. Among all patients, 77 men had a tPSA level between 4 and 10 ng/mL. PCa at the initial biopsy was detected in 45% (63/140) of the patients. Among 63 patients diagnosed with PCa, 15 (23.8%) had GS 6 disease, 18 (28.6%) had GS 7 disease, and 30 (47.6%) had GS \geq 8 disease.

Patients with PCa showed significantly higher age, tPSA, %p2PSA, and PHI than those without PCa at biopsy. Conversely, %fPSA levels were significantly higher in patients without PCa. However, the fPSA concentration did not differ between the two groups.

In 77 patients with a tPSA level between 4 and 10 ng/mL, %p2PSA and PHI were significantly different between groups with and without PCa (Table 2). However, the median tPSA, %fPSA, and p2PSA levels did not differ between the two groups.

In the PCa group, 48 (76.2%) patients with GS \geq 7 showed significantly higher %p2PSA (3.17% vs. 1.26%, $p < 0.001$) and PHI (120.8 vs. 35.4, $p < 0.001$) than those with GS 6 disease (Table 3). Patients with GS \geq 7 had a more positive core number (6.0 vs. 3.0, $p = 0.032$)

In 140 patients, the AUC for tPSA, fPSA, %fPSA, p2PSA, %p2PSA, and PHI were 0.63, 0.57, 0.69, 0.69, 0.71, and 0.75, respectively (Fig. 1).

Using tPSA as a standard, the AUC was significantly greater in the PHI group ($p = 0.005$). Both %p2PSA and PHI were strong independent predictive markers ($p < 0.001$, $p < 0.001$) and significantly increased the predictive accuracy of a base multivariable model including age, tPSA, and %fPSA using multivariate logistic regression analysis (Table 4).

Similarly, in the subgroup of patients with tPSA 4–10 ng/mL, both %p2PSA and PHI were strong independent predictors ($p = 0.031$, $p = 0.027$) and showed significantly improved predictive accuracy in addition to a base multivariable model using multivariate logistic regression analysis. ($p = 0.015$, $p = 0.010$, Table 5).

In Table 6, the results of univariate and multivariable logistic regression analyses identifying the predictors of PCa with a Gleason score \geq 7 are presented. %p2PSA and PHI significantly improved the predictive accuracy of a base multivariable model. ($p < 0.001$, $p < 0.001$).

Table 7 shows the number of patients in whom unnecessary biopsies could be avoided and the number and pathologic characteristics of cancers that would be missed using %fPSA, p2PSA, %p2PSA, and PHI at a cutoff level with 90% sensitivity in the subgroup with tPSA 4–10 ng/mL and the entire population, respectively.

At a cutoff PHI value of 33.4, 22.9% (32/140) of patients could have avoided unnecessary biopsies without missing any significant aggressive cancers (GS ≥ 7). In the subgroup with tPSA 4–10 ng/mL, the use of %p2PSA (12/77, 15.5%) and PHI (9/77, 11.7%) could have avoided unnecessary biopsy and prevented missing more significant aggressive cancers, without missing patients with aggressive cancers.

Patients with aggressive cancers had higher PHI scores. The median values of the PHI score showed a stepwise increase along the Gleason score more obviously compared to the other markers (Fig. 2).

Discussion

This study evaluated the usefulness of %p2PSA and PHI in 140 subjects, and our findings support previous results regarding both biomarkers. %p2PSA and PHI showed higher predictive performance in the detection of PCa than standard reference methods and the ability to distinguish aggressive (GS ≥ 7) from clinically indolent state of PCa. Thus, their use could avoid unnecessary biopsies without missing clinically significant cancers.

Currently, PSA is widely used for PCa screening, but the limitations of PSA as a biomarker for PCa detection have been well demonstrated. It is necessary to distinguish PCa from benign prostatic disease and to clarify the aggressiveness of cancers, but PSA cannot completely predict the presence and biological behavior of PCa [13]. The early detection of PCa using PSA results in a large number of negative biopsies and a high proportion of patients diagnosed with clinically low aggressive tumors (over-diagnosis) followed by unnecessary treatment (over-treatment) and morbidity related to complications [14, 15]. Thus, a more specific biomarker that could increase predictive accuracy and risk stratification properties is needed to identify patients who may have PCa and reduce morbidity due to unnecessary diagnosis and treatment.

The usefulness of %p2PSA and PHI in the detection of PCa has been studied extensively in recent years. The biomarkers improve the specificity of tPSA for PCa detection and are associated with a more aggressive state of disease [5, 13].

Catalona *et al.* demonstrated that high PHI level was associated with increased detection rate of PCa in subjects with a tPSA level between 2 and 10 ng/ml in a prospective multi-institutional study [16]. Jansen *et al.* showed that PHI showed significantly superior performance than PSA and %fPSA for PCa prediction, and the involvement of p2PSA in a base multivariable model significantly improved the predictive value and specificity of PCa [17].

Several studies have also validated the usefulness of PHI in Asian countries. Chiu *et al.* in their prospective study showed that the PHI improved the diagnostic accuracy compared with PSA-based predictive models in 569 subjects with PSA levels between 4 and 10 ng/mL in Hong Kong [18]. Na *et al.* in a multicenter study in Shanghai demonstrated superior diagnostic accuracy of PHI compared to tPSA

both in subjects with a PSA level between 2.1 and 10 ng/mL and in those with a PSA level > 10 ng/mL [19].

One meta-analysis showed that %p2PSA and PHI improved diagnostic performance compared to tPSA and %fPSA consistently in detecting PCa and can reduce unnecessary biopsies [20]. In addition, a European prospective study showed that PHI showed improved predictive performance for GS \geq 7 PCa [21]. The European Association of Urology as per the 2016 guidelines suggested that the PHI could be considered as an additional diagnostic method for patients with PSA levels of 2–10 ng/mL and a negative DRE [22].

In the current study, the addition of %p2PSA or PHI to a predictive base multivariate regression model significantly increased its predictive accuracy. Moreover, %p2PSA and PHI were associated with aggressiveness of PCa and could improve the predictive performance of the base model for detecting GS \geq 7 PCa. The proportion of aggressive cancer was mostly associated with the PHI level among these markers. At a cutoff PHI value of 33.4, 22.9% (32/140) of biopsies would have been avoided without missing any significant aggressive cancers (GS \geq 7). In the same context, at a cutoff PHI value of 26.3, 11.7% (9/77) of biopsies would have been avoided without missing any significant aggressive cancers (GS \geq 7) in subjects with tPSA 4–10 ng/mL. Similarly, another study demonstrated that 15.5%–45.2% of their group could have avoided unnecessary biopsy at a cut-off of PHI score 25–32, although they would have missed 1.1%–3.8% of significant aggressive cancers [23, 24].

The European population had a fourfold higher incidence of PCa than the Asian population, while age and PSA level showed a tendency to be higher among Asians in a previous study [25]. Korean men also have a lower incidence rate of PCa than the Western population, but PCa in the Korean population shows worse characteristics of the disease compared to Western men [3, 4]. Most of the previously reported data regarding %p2PSA and PHI have been collected mainly in Western groups; therefore, it is necessary to verify the usefulness of these biomarkers in Korean groups. Kim *et al.* evaluated the clinical predictive value of %p2PSA and PHI in Korean men [26]. Similar to previous studies, they suggested that the diagnostic accuracy of PHI was better than that of tPSA in the Korean population.

Recently, multiparametric magnetic resonance imaging (MRI) has improved the detection rate of potentially significant PCa [27], but it generally requires higher costs and radiological expertise. It has been reported that MRI and PHI are complementary to each other for detecting significant PCa [28]. PHI is a blood test that can be performed simply and is ordered by general practitioners, and there is no need for radiologic interpretation. In the future, as the cost of a blood test will probably decrease, PHI will be widely used as a screening tool for PCa.

This study has several limitations. First, it was performed in a single tertiary center and had a relatively small sample size. Second, not all patients in our study underwent radical prostatectomy; therefore, we could not inspect the occurrence of Gleason upgrading after prostatectomy. In addition, we did not inspect the percentage of tumor involvement in each biopsy core and tumor size. Finally, we did not use

multiparametric MRI. MRI could help guide more accurate localization for biopsy and increase the performance for detecting significant PCa.

Conclusions

Our findings suggest that the diagnostic performance of %p2PSA and PHI to predict the presence and aggressiveness of PCa was superior to that of PSA and %fPSA in the Korean population. Using PHI, a high proportion of unnecessary biopsies could be avoided. Further research is needed to support these results.

List Of Abbreviations

AUC, area under the curve; fPSA, free PSA; GS, Gleason score; p2PSA, [-2]proPSA; PCa, prostate cancer; PHI, prostate health index; PSA, prostate-specific antigen; ROC, receiver operating characteristic; tPSA, total PSA

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of the Sanngye Paik Hospital, Inje University. (Committee reference number: 2016-04-022). All participants provided written informed consent before participation in the study.

Consent for publication

Written informed consent was obtained from every patient for publication of this research report.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supports by a grant form Research year of Inje University in 2011.

Authors' contributions

S.J. Yoo, J.Y. Kim and J.H. Yu have made substantial contributions to conception and design, or acquisition of data. J.Y. Kim, L.H. Sung, D.Y. Cho performed the analysis and interpretation of data. J.Y. Kim, S.J. Yoo have been involved in drafting the manuscript or revising it critically for important intellectual content. H.J. Kim performed the histological examination of the specimens. And all authors have given final approval for the manuscript to be published.

Acknowledgements

The authors thank all our participants for their gracious participation in this study.

References

1. Siegel RL, Miller KD, Jemal A: **Cancer statistics, 2020.** *CA Cancer J Clin* 2020, **70**(1):7-30.
2. Han HH, Park JW, Na JC, Chung BH, Kim CS, Ko WJ: **Epidemiology of prostate cancer in South Korea.** *Prostate Int* 2015, **3**(3):99-102.
3. Kang DI, Chung JI, Ha HK, Min K, Yoon J, Kim W, Seo WI, Kang P, Jung SJ, Kim IY: **Korean prostate cancer patients have worse disease characteristics than their American counterparts.** *Asian Pac J Cancer Prev* 2013, **14**(11):6913-6917.
4. Song C, Kang T, Ro JY, Lee MS, Kim CS, Ahn H: **Nomograms for the prediction of pathologic stage of clinically localized prostate cancer in Korean men.** *J Korean Med Sci* 2005, **20**(2):262-266.
5. Saini S: **PSA and beyond: alternative prostate cancer biomarkers.** *Cell Oncol (Dordr)* 2016, **39**(2):97-106.
6. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, Bray F: **International variation in prostate cancer incidence and mortality rates.** *Eur Urol* 2012, **61**(6):1079-1092.
7. Etzioni R, Penson DF, Legler JM, di Tommaso D, Boer R, Gann PH, Feuer EJ: **Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends.** *J Natl Cancer Inst* 2002, **94**(13):981-990.
8. McGrath S, Christidis D, Perera M, Hong SK, Manning T, Vela I, Lawrentschuk N: **Prostate cancer biomarkers: Are we hitting the mark?** *Prostate Int* 2016, **4**(4):130-135.
9. Mikolajczyk SD, Catalona WJ, Evans CL, Linton HJ, Millar LS, Marker KM, Katir D, Amirkhan A, Rittenhouse HG: **Proenzyme forms of prostate-specific antigen in serum improve the detection of prostate cancer.** *Clin Chem* 2004, **50**(6):1017-1025.
10. Hori S, Blanchet JS, McLoughlin J: **From prostate-specific antigen (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer.** *BJU Int* 2013, **112**(6):717-728.
11. Filella X, Gimenez N: **Evaluation of [-2] proPSA and Prostate Health Index (phi) for the detection of prostate cancer: a systematic review and meta-analysis.** *Clin Chem Lab Med* 2013, **51**(4):729-739.
12. Lazzeri M, Haese A, Abrate A, de la Taille A, Redorta JP, McNicholas T, Lughezzani G, Lista G, Larcher A, Bini V *et al.*: **Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA)**

and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheS project. *BJU Int* 2013, **112**(3):313-321.

13. Hatakeyama S, Yoneyama T, Tobisawa Y, Ohyama C: Recent progress and perspectives on prostate cancer biomarkers. *Int J Clin Oncol* 2017, **22**(2):214-221.
14. Borghesi M, Ahmed H, Nam R, Schaeffer E, Schiavina R, Taneja S, Weidner W, Loeb S: Complications After Systematic, Random, and Image-guided Prostate Biopsy. *Eur Urol* 2017, **71**(3):353-365.
15. Heijnsdijk EA, Wever EM, Auvinen A, Hugosson J, Ciatto S, Nelen V, Kwiatkowski M, Villers A, Paez A, Moss SM *et al*: Quality-of-life effects of prostate-specific antigen screening. *N Engl J Med* 2012, **367**(7):595-605.
16. Catalona WJ, Partin AW, Sanda MG, Wei JT, Klee GG, Bangma CH, Slawin KM, Marks LS, Loeb S, Broyles DL *et al*: A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. *J Urol* 2011, **185**(5):1650-1655.
17. Jansen FH, van Schaik RH, Kurstjens J, Horninger W, Klocker H, Bektic J, Wildhagen MF, Roobol MJ, Bangma CH, Bartsch G: Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection. *Eur Urol* 2010, **57**(6):921-927.
18. Chiu PK, Roobol MJ, Teoh JY, Lee WM, Yip SY, Hou SM, Bangma CH, Ng CF: Prostate health index (PHI) and prostate-specific antigen (PSA) predictive models for prostate cancer in the Chinese population and the role of digital rectal examination-estimated prostate volume. *Int Urol Nephrol* 2016, **48**(10):1631-1637.
19. Na R, Ye D, Qi J, Liu F, Helfand BT, Brendler CB, Conran CA, Packiam V, Gong J, Wu Y *et al*: Prostate health index significantly reduced unnecessary prostate biopsies in patients with PSA 2-10 ng/mL and PSA >10 ng/mL: Results from a Multicenter Study in China. *The Prostate* 2017, **77**(11):1221-1229.
20. Wang W, Wang M, Wang L, Adams TS, Tian Y, Xu J: Diagnostic ability of %p2PSA and prostate health index for aggressive prostate cancer: a meta-analysis. *Sci Rep* 2014, **4**:5012.
21. Guazzoni G, Nava L, Lazzeri M, Scattoni V, Lughezzani G, Maccagnano C, Dorigatti F, Ceriotti F, Pontillo M, Bini V *et al*: Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting. *Eur Urol* 2011, **60**(2):214-222.
22. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, Fossati N, Gross T, Henry AM, Joniau S *et al*: EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur Urol* 2017, **71**(4):618-629.
23. Lazzeri M, Haese A, de la Taille A, Palou Redorta J, McNicholas T, Lughezzani G, Scattoni V, Bini V, Freschi M, Sussman A *et al*: Serum isoform [-2]proPSA derivatives significantly improve prediction of

prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: a multicentric European study.
Eur Urol 2013, **63**(6):986-994.

24. Filella X, Foj L, Augé JM, Molina R, Alcover J: **Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer.** *Clin Chem Lab Med* 2014, **52**(9):1347-1355.
25. Wong M, Yip C, Li H, Tan T, Kanesvaran R, Chowbay B, Tan PH, Tan MH, Wong FY: **Assessment of the American Joint Committee on Cancer 7th edition staging for localised prostate cancer in Asia treated with external beam radiotherapy.** *Annals of the Academy of Medicine, Singapore* 2014, **43**(10):484-491.
26. Park H, Lee SW, Song G, Kang TW, Jung JH, Chung HC, Kim SJ, Park CH, Park JY, Shin TY *et al:* **Diagnostic Performance of %[-2]proPSA and Prostate Health Index for Prostate Cancer: Prospective, Multi-institutional Study.** *J Korean Med Sci* 2018, **33**(11):e94.
27. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, Collaco-Moraes Y, Ward K, Hindley RG, Freeman A *et al:* **Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study.** *Lancet* 2017, **389**(10071):815-822.
28. Druskin SC, Tosoian JJ, Young A, Collica S, Srivastava A, Ghabili K, Macura KJ, Carter HB, Partin AW, Sokoll LJ *et al:* **Combining Prostate Health Index density, magnetic resonance imaging and prior negative biopsy status to improve the detection of clinically significant prostate cancer.** *BJU Int* 2018, **121**(4):619-626.

Tables

Table 1. Demographic and clinical characteristics of all study subjects who underwent the first prostate biopsy

	Total	No cancer	Cancer	P value
	N, 140	N, 77 (55%)	N, 63 (45%)	-
<i>Median (interquartile range)</i>				
Age, yr	69.0 (10.0)	67.0 (9.0)	72.0 (10.0)	0.001
tPSA, ng/mL	6.93 (6.05)	6.45 (3.8)	8.18 (15.3)	0.010
fPSA	1.03 (0.92)	0.92 (0.8)	1.07 (1.4)	0.160
%fPSA	14.55 (9.29)	17.13 (8.0)	11.16 (9.0)	0.003
p2PSA, pg/mL	19.18 (30.97)	15.54 (16.7)	31.06 (58.6)	<0.001
%p2PSA	2.02 (2.21)	1.57 (1.5)	2.83 (2.6)	<0.001
PHI	45.90 (82.72)	39.54 (38.0)	91.18 (147.9)	<0.001
Positive core number	-	-	5.0 (7.0)	-
<i>Number (percentage)</i>				
GS 6	-	-	15 (23.8%)	-
GS 7			18 (28.6%)	-
GS ≥8			30 (47.6%)	-

PSA = prostate-specific antigen, tPSA = total PSA, fPSA = free PSA, p2PSA = [2]proPSA, PHI = prostate health index, GS = Gleason score

Table 2. Descriptive characteristics of subjects with tPSA 4–10 ng/mL

	Total	No cancer	Cancer	P value
	N, 77	N, 48 (62.3%)	N, 29 (37.7%)	-
<i>Median (interquartile range)</i>				
Age, yr	68.0 (12.0)	66.5 (11.0)	71.0 (12.0)	0.010
tPSA, ng/mL	6.41 (2.5)	6.42 (2.3)	6.13 (2.8)	0.877
fPSA	0.92 (0.5)	0.97 (0.6)	0.92 (2.4)	0.185
%fPSA	15.49 (8.6)	16.83 (7.5)	13.04 (7.1)	0.284
p2PSA, pg/mL	16.86 (17.5)	15.34 (16.1)	17.09 (23.7)	0.189
%p2PSA	1.61 (1.6)	1.50 (1.0)	2.35 (2.6)	0.015
PHI	41.35 (37.9)	39.65 (28.9)	53.72 (56.8)	0.018
Positive core number	-	-	4.0 (7.0)	-
<i>Number (percentage)</i>				
GS 6	-	-	9 (31%)	-
GS 7			10 (34.5%)	-
GS ≥8			10 (34.5%)	-

PSA = prostate-specific antigen, tPSA = total PSA, fPSA = free PSA, p2PSA = [2]proPSA, PHI = prostate health index, GS = Gleason score

Table 3. Comparison between GS 6 disease and more aggressive disease in PCa patients

	GS 6	GS \geq 7	Pvalue
	N, 15 (23.8%)	N, 48 (76.2%)	-
<i>Median (interquartile range)</i>			
Age, yr	73.0 (9.0)	72.0 (12.0)	0.520
tPSA, ng/mL	7.47 (4.6)	9.75 (23.6)	0.156
fPSA	0.97 (0.6)	1.13 (1.7)	0.358
%fPSA	13.08 (8.0)	10.98 (9.2)	0.302
p2PSA, pg/mL	13.9 (13.4)	45.3 (72.6)	0.001
%p2PSA	1.26 (1.0)	3.17 (2.2)	<0.001
PHI	35.4 (28.0)	120.8 (148.6)	<0.001
Positive core number	3.0 (4.0)	6.0 (6.0)	0.032

PSA = prostate-specific antigen, tPSA = total PSA, fPSA = free PSA, p2PSA = [2]proPSA, PHI = prostate health index, GS = Gleason score

Table 4. Logistic regression analyses predicting the probability of prostate cancer.

Predictors	AUC of individual predictor variable (95% CI); P value*	Bivariate analysis OR(95%CI); P value	Multivariate analysis		
			Base model**	Base model + %p2PSA	Base model + PHI
tPSA, ng/mL	0.63 (0.54 - 0.71) -	1.100 (1.04–1.16); 0.001	1.084 (0.98–1.20); 0.137	1.067 (0.97 –1.18); 0.197	1.030 (0.94–1.13); 0.514
fPSA	0.57 (0.48 - 0.65) 0.117	1.543 (1.06–2.25); 0.024	1.017 (0.50–2.09); 0.962	1.015 (0.51–2.04); 0.966	0.898 (0.47–1.72); 0.745
%fPSA	0.69 (0.61 - 0.77) 0.203	0.927 (0.88–0.98); 0.004	0.961 (0.89–1.04); 0.330	0.965 (0.89–1.04); 0.357	0.975 (0.91–1.05); 0.507
p2PSA, pg/mL	0.69 (0.60 - 0.76) 0.157	1.021 (1.01–1.04); 0.001	-	-	-
%p2PSA	0.71 (0.63 - 0.78) 0.155	1.612 (1.26–2.07); 0.001	-	1.432 (1.11–1.84); 0.005	-
PHI	0.75 (0.67 - 0.82) 0.005	1.015 (1.01–1.02); 0.001	-	-	1.013 (1.00–1.02); 0.004
AUC of multivariate models (95% CI);	-	-	0.691 (0.60–0.78)	0.757 (0.68–0.84)	0.765 (0.69–0.84)
Gain in predictive accuracy (95% CI);	-	-	-	0.066 (0.02–0.11);	0.074 (0.02–0.12);
P value				<0.001	<0.001

*P value : Comparison of AUC using tPSA as standard

**Base model includes age, tPSA, and %fPSA.

AUC, area under the receiver operating characteristic curve; PSA, prostate-specific antigen; fPSA, free PSA; p2PSA, [-2]proPSA; PHI, prostate health index; tPSA, total PSA

OR = odds ratio, CI = confidence interval.

Table 5. Logistic regression analyses predicting the probability of prostate cancer in subjects with tPSA 4–10 ng/mL

Predictors	AUC of individual predictor variable (95% CI); P value*	Bivariate analysis OR(95%CI); <i>P</i> value	Multivariate analysis		
			Base model OR (95%CI); <i>P</i> value	Base model + %p2PSA OR (95%CI); <i>P</i> value	Base model + PHI OR(95%CI); <i>P</i> value
tPSA, ng/mL	0.50 (0.38 - 0.61) -	1.024 (0.76 – 1.38); 0.875	1.486 (0.67 – 3.30); 0.330	1.147 (0.48 – 2.75); 0.758	1.065 (0.44 – 2.58); 0.888
fPSA	0.59 (0.47 -0.70) 0.418	0.529 (0.18 – 1.53); 0.240	0.057 (0.00 – 9.73); 0.275	0.200 (0.00 – 47.1); 0.564	0.216 (0.00 – 51.3); 0.583
%fPSA	0.63 (0.52 - 0.74) 0.090	0.961 (0.89 – 1.03); 0.284	1.161 (0.82 – 1.64); 0.394	1.076 (0.75 – 1.54); 0.689	1.071 (0.75 – 1.53); 0.706
p2PSA, pg/mL	0.59 (0.47 - 0.70) 0.286	1.023 (1.00 – 1.05); 0.089	-	-	-
%p2PSA	0.67 (0.55 - 0.77) 0.075	1.539 (1.09- 2.16); 0.031	-	1.529 (1.08 – 2.17); 0.035	-
PHI	0.69 (0.55 - 0.78) 0.054	1.015 (1.00 – 1.03); 0.027	-	-	1.015 (1.00 – 1.03); 0.027
AUC of multivariate models (95% CI);	-	-	0.594 (0.47 – 0.72)	0.683 (0.56 – 0.80)	0.695 (0.55 – 0.80)
Gain in predictive accuracy (95% CI); <i>P</i> value	-	-	-	0.089 (0.02 – 0.14);	0.101 (0.07 – 0.17);

0.015

0,010

*P value : Comparison of AUC using tPSA as standard

**Base model includes age, tPSA, and %fPSA.

AUC, area under the receiver operating characteristic curve; PSA, prostate-specific antigen; fPSA, free PSA; p2PSA, [-2]proPSA; PHI, prostate health index; tPSA, total PSA

OR = odds ratio, CI = confidence interval.

Table 6. Logistic regression analyses predicting the probability of Gleason score ≥ 7 disease

Predictors	AUC of individual predictor variable (95% CI); P value*	Bivariate analysis OR(95%CI); <i>P</i> value	Multivariate analysis		
			Base model	Base model + %p2PSA	Base model + PHI
tPSA, ng/mL	0.62 (0.48 - 0.77) 0.156	1.064 (0.99–1.14); 0.086	1.031 (0.92–1.16); 0.601	1.022 (0.95–1.11); 0.583	0.978 (0.91–1.06); 0.572
	0.58 (0.44 - 0.72) 0.358	1.818 (0.84–3.94); 0.129	1.413 (0.39–5.11); 0.598	0.962 (0.34–2.74); 0.942	0.745 (0.28–2.00); 0.559
%fPSA	0.41 (0.26 - 0.57) 0.302	0.973 (0.91–1.04); 0.440	0.977 (0.88–1.09); 0.678	0.989 (0.87–1.12); 0.861	1.014 (0.90–1.14); 0.814
	0.79 (0.68 - 0.91) 0.001	1.047 (1.01–1.09); 0.017	-	-	-
%p2PSA	0.87 (0.75 - 0.99) <0.001	3.887 (1.73–8.74); 0.009	-	3.530 (1.50–8.34); 0.021	-
	0.88 (0.76 - 0.99) <0.001	1.020 (1.01–1.04); 0.007	-	-	1.028 (1.01–1.05); 0.015
AUC of multivariate models (95% CI)		-	0.640 (0.49–0.79)	0.879 (0.76–1.00)	0.881 (0.73–0.99)
Gain in predictive accuracy (95% CI); <i>P</i> value		-	-	0.239 (0.10–0.26);	0.241 (0.10–0.27);

<0.001

<0.001

*P value : Comparison of AUC using tPSA as standard

**Base model includes age, tPSA, and %fPSA.

AUC, area under the receiver operating characteristic curve; PSA, prostate-specific antigen; fPSA, free PSA; p2PSA, [-2]proPSA; PHI, prostate health index; tPSA, total PSA

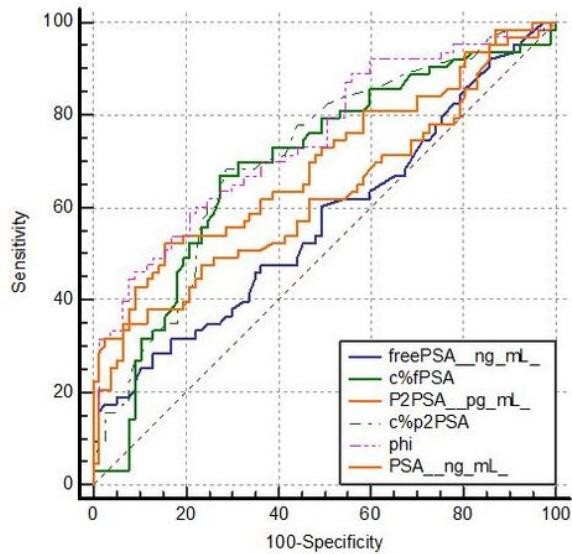
OR = odds ratio, CI = confidence interval.

Table 7. The number of biopsies that could be avoided and characteristics of missed cancers at cut-off of 90% sensitivity of the markers in subjects with tPSA 4–10 ng/mL

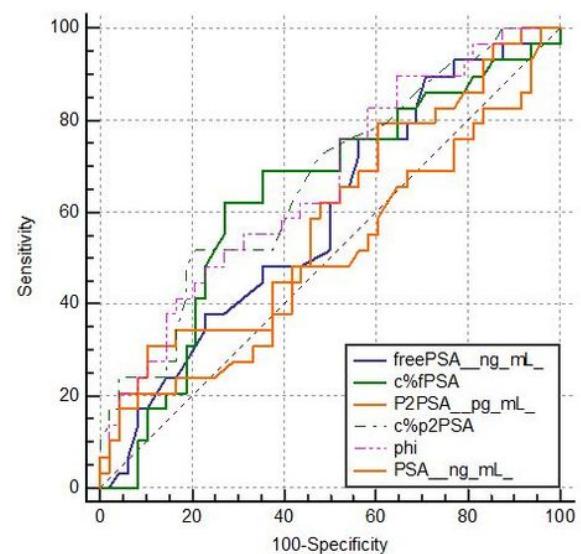
Marker	Cut-off at 90% sensitivity	% Specificity	Unnecessary biopsy avoided	Missed cancer			
				Total	Missed GS 6	Missed GS 7	Missed GS \geq 8
Total PSA 4–10 ng/mL							
%fPSA	≤ 7.86	9%	4 (5.2%)	3 (10.3%)	0 (0%)	1 (3.5%)	2 (6.8%)
p2PSA	≥ 8.08 (pg/mL)	17%	7 (9.1%)	3 (10.3%)	2 (6.8%)	0 (0%)	1 (3.5%)
% p2PSA	≥ 1.20	27%	12 (15.5%)	3 (10.3%)	3 (10.3%)	0 (0%)	0 (0%)
PHI	≥ 26.33	25%	9 (11.7%)	2 (6.8%)	2 (6.8%)	0 (0%)	0 (0%)
All study subjects							
%fPSA	≤ 6.42	7%	6 (4.3%)	7 (11.1%)	0 (0%)	2 (3.2%)	5 (7.9%)
p2PSA	≥ 8.07 (pg/mL)	20%	16 (11.4%)	7 (11.1%)	4 (6.3%)	2 (3.2%)	1 (1.6%)
% p2PSA	≥ 1.22	31%	24 (17.1%)	7 (11.1%)	7 (11.1%)	0 (0%)	0 (0%)
PHI	≥ 33.40	40%	32 (22.9%)	5 (7.9%)	5 (7.9%)	0 (0%)	0 (0%)

PSA, prostate-specific antigen; fPSA, free PSA; p2PSA, [-2]proPSA; PHI, prostate health index

Figures



(A)



(B)

Figure 1

ROC curves depicting the accuracy of individual predictors of prostate cancer. (A) ROC curves in all subjects. (B) ROC curves in subjects with tPSA 4–10 ng/mL. PSA, prostate-specific antigen; fPSA, free PSA; p2PSA, [-2]proPSA; PHI, prostate health index; ROC, receiver operating characteristic; tPSA, total PSA

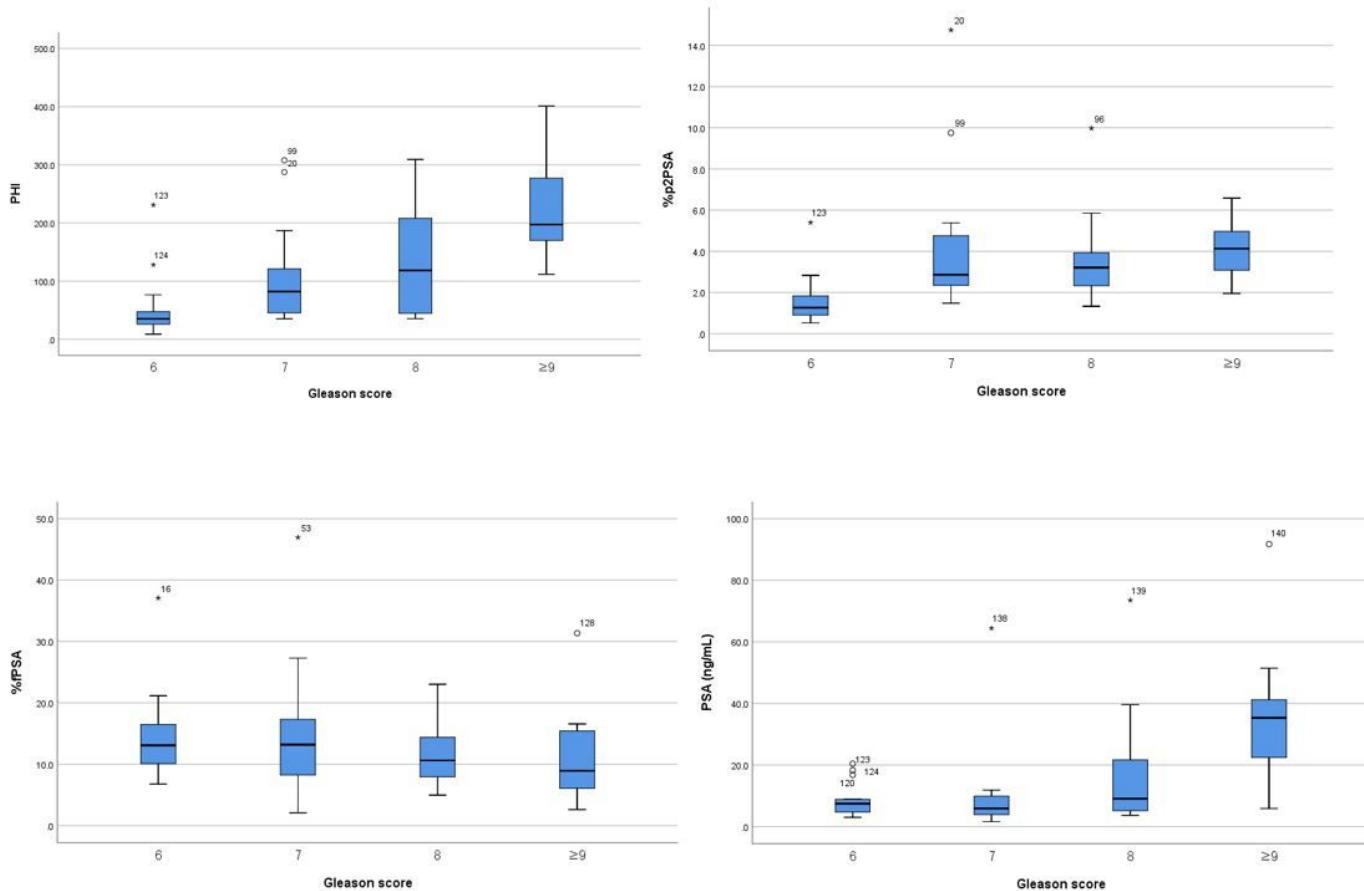


Figure 2

Box plots comparing PHI, %p2PSA, %fPSA and tPSA in relation to a biopsy Gleason score. PSA, prostate-specific antigen; fPSA, free PSA; p2PSA, [-2]proPSA; PHI, prostate health index; tPSA, total PSA